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MALARIA

ITS CAUSE, PREVENTION AND CURE

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By
W. E. DEEKS, M.D.

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MALARIA

Its Cause, Prevention and Cure

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By

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INTRODUCTION

Malaria is widely distributed throughout the littoral and other low-lying areas of tropical and subtropical countries of the world, wherever the rainfall is sufficient to leave standing water in which anopheles mosquitoes can breed. The extreme latitudes where it has been encountered are 40° South and 60° North.

Our knowledge of the clinical manifestation of malaria goes back to antiquity. Hippocrates differentiated malaria fevers from continuous fevers, and recognized the periodicity of the malarial paroxysms, dividing them into quotidian, tertian and quartan.

No specific remedy for the treatment of malaria was known in Europe until 1640, when the Countess del Cinchon introduced cinchona bark, which was named after her. As the wife of the Viceroy of Peru, in 1638 she had been cured of an intermittent fever by a preparation composed of this bark. And today the only specific remedy known for the cure of malaria is quinine and its derivatives prepared from cinchona bark.

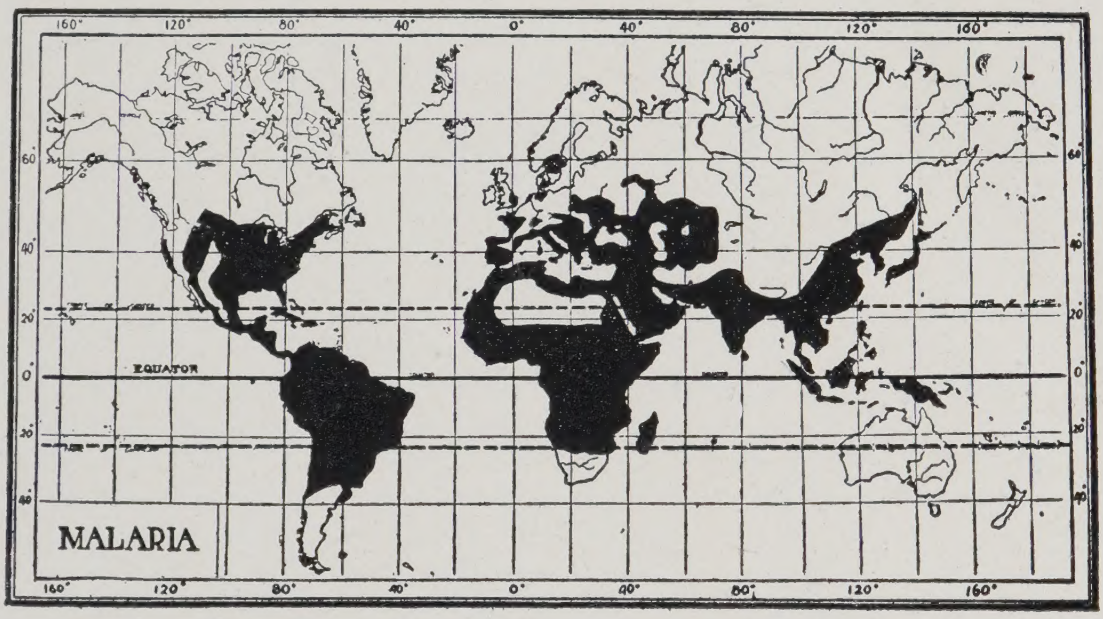
In 1880 Laveran discovered the parasites of malaria under the microscope. In 1894 Manson suggested the theory that the disease was transmitted by mosquitoes. And in 1898 Ross definitely incriminated the anopheles mosquitoes as the transmitting agents.

In addition to these outstanding discoveries, increments to our knowledge have been added by a large number of scientific workers, and today most of the facts concerning the causation, prevention and cure of malaria are known. With our present knowledge, there is no reason why an intelligent man, familiar with the data and the means available to protect himself, should contract malaria. Enormous areas throughout the world where malaria was at one time endemic have been so far freed from infection that it has ceased to be a serious problem, and in many of those areas malaria no longer exists.

These results have been obtained largely through drainage and cultivation of the soil. By these methods the breeding places of mosquitoes have been destroyed, and with the consequent reduction of malaria the tillers of the soil have become more efficient and are receiving greater returns for labor expended. This state of affairs begets health and prosperity, which, in turn, mean more comfortable homes, better food and clothes, improved educational facilities and, in short,

an advance in the physical and mental status of the inhabitants of the farming communities, so that they are able to help themselves. We must direct our efforts to an extension of such methods as these to districts now infected, if we are to obtain satisfactory results.

Malaria districts should be investigated by agricultural experts, and the farmers should be advised as to what crops can be most advantageously cultivated to give them the best results for labor expended. Naturally, there is no use of raising good crops if there are no roads over which to transport them, and no market available to absorb the produce. To this end, state and federal assistance is necessary. Precedents have been established by the reclamation of large, uninhabited areas for agricultural purposes. Is it not just as commendable, and infinitely more humanitarian, to spend money for the reclamation of large *inhabited* areas, and thus reclaim not only the land but the inhabitants also? The inhabitants are the chief asset of



GEOGRAPHICAL DISTRIBUTION OF MALARIA (STITT)

any country. Through the results of their labor prosperity comes, and the more efficient they are, the greater the returns.

At present, the fight against malaria is being carried on largely by individual corporations and beneficent organizations. They are waging an uphill fight, however, and their efforts to give the best results need governmental support. If we enable the farmer to become prosperous, furnish him with school facilities, educate him in matters relating to the prevention of diseases immediately concerning him—in other words, give him a square deal and afford him an opportunity to help himself, the problem of malaria-control will be solved.

A large number of people in tropical and subtropical countries labor under the delusion that all febrile conditions are malarial in origin, and take quinine indefinitely irrespective of the results. This is a great mistake. Any fever which does not yield to quinine in proper

dosage within from 4 to 6 days is probably not due to malaria, but has some other underlying cause. I wish, therefore, to emphasize the importance of consulting a physician in all cases of fever which do not yield rapidly to the administration of quinine.

This little brochure is an attempt to place the main facts concerning the cause, prevention and cure of malaria before physicians, sanitarians, social workers, school teachers and intelligent laymen who wield a large local influence in their respective communities to the end that they, having informed themselves, may enlighten others.

In preparation of this pamphlet I am indebted to Doctors Milton J. Rosenau, H. R. Carter, S. T. Darling, L. D. Fricks and J. A. Ferrell, who kindly read the manuscript and made important suggestions.

For illustrations, I am indebted to Surgeon-General E. R. Stitt and his publishers, P. Blakiston's Son & Company; to Professor F. Fülleborn, of Hamburg, Germany; Dr. J. G. Thomson, of London, England; Vittorio Ascoli, Bureau of Entomology, U. S. Department of Agriculture; American Museum of Natural History; and Miss Mabel Hedge, of the Rockefeller Institute.

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General Manager
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17 Battery Place
New York City

February 16, 1925

MALARIA

ITS CAUSE, PREVENTION AND CURE

MALARIA is a disease caused by three closely related species of minute animal parasites. There are two distinct cycles in their development, one of which, the *nonsexual*, takes place in man, in whom it causes the disease known as malaria; the other, the *sexual* cycle, takes place in the female anopheles mosquito.

Nonsexual Cycle of Development of the Parasite

When the young parasites (sporozoites) are injected into the blood of a human being by the malaria-infected mosquito, while feeding on that individual, they immediately invade the red cells on which they feed and in which they grow, until the contents of the invaded red cells are consumed. This process takes from 48 to 72 hours, the length of time depending on the species of parasite involved. During this period the parasites have reached maturity, and each one has become divided into a number of minute bodies, known as "spores." The spores in lower forms of animal and plant life correspond, in function, to the seeds of the grass family and to the nuts or seeds of fruit trees. Each spore, seed or nut is capable, under suitable conditions, of growing into a new organism, grass-plant, or tree. By "sporulation" is meant the rupture of the sac containing the spores, which are thus liberated.

The size of the parasite can be best appreciated when we consider that a red-blood cell, in which one or more parasites develop, is approximately 1/3,200 of an inch in diameter and about one quarter of that size in thickness, or approximately 1/12,800 of an inch. There are about 5,000,000 red cells in a cubic millimeter* of normal blood, and to these the blood owes its red color.

The number of the spores produced by each nonsexual malaria parasite varies from 8 to 32, and they entirely replace the contents of a red cell; its wall or limiting membrane alone remains. This wall then ruptures, liberating the spores in the "plasma," or fluid contents,

*A millimeter equals about 1/25 of an inch.

of the blood. Some of the spores are "phagocyted," or engulfed, by the white cells of the blood (this process being one means of getting rid of foreign or dead material in our bodies) and all the spores not destroyed by this and other defensive agencies of the body invade other red cells, and repeat the same method of growth—spore-formation and sporulation—until, by geometrical progression, enormous numbers of parasites develop.

At each sporulation a toxin, or poison, is liberated, and this is responsible for most of the symptoms produced. Coincident with the nonsexual development of the parasites, sexual forms of the organisms, (gametes, or gametocytes), male and female, are developing in the red cells. They require about twice as long as the nonsexual forms to reach maturity. They do not divide and form spores; but when mature, each one completely occupies a red cell. Their number is much smaller than that of the nonsexual parasites, and Darling estimates that about 12 must be present in a cubic millimeter of blood before the number is sufficient to infect mosquitoes.

The Sexual Cycle of the Parasites

The female anopheles mosquito must have a meal of warm blood in order to mature her eggs, and man serves the purpose; but some species will feed about as readily on any other warm-blooded animal, domestic or wild. When feeding upon a malaria-infected individual, the female anopheles takes into her stomach, along with the blood, large numbers of parasites, both sexual and nonsexual. The latter are digested and disappear, but the sexual forms develop. The male gamete, or sexual element, throws out some threadlike extensions (flagella) one of which enters a female gamete after the latter has undergone some changes to make room for it, and thus the female becomes fertilized and proceeds to further development. A worm-like body (zygote) soon develops which is able to bore through the mosquito's delicate stomach wall, and there it assumes a globular form (oöcyst), gradually enlarges, and in from 7 to 20 days, according to the surrounding temperature, becomes mature. Cold weather delays development, and warm weather favors it.

At maturity this body, or oöcyst, has become divided up into hundreds or thousands of slender, slightly curved, elongated bodies, called "sporozoites." The wall of the mature oöcyst then ruptures, liberating the sporozoites into all parts of the body cavity of the mosquito, whence they make their way into her salivary glands, and there they are ready to be injected into and to infect the next human individual on whom she feeds. A female infected mosquito may live 6 months, and for at least 2 months subsequent to infection may be able to trans-

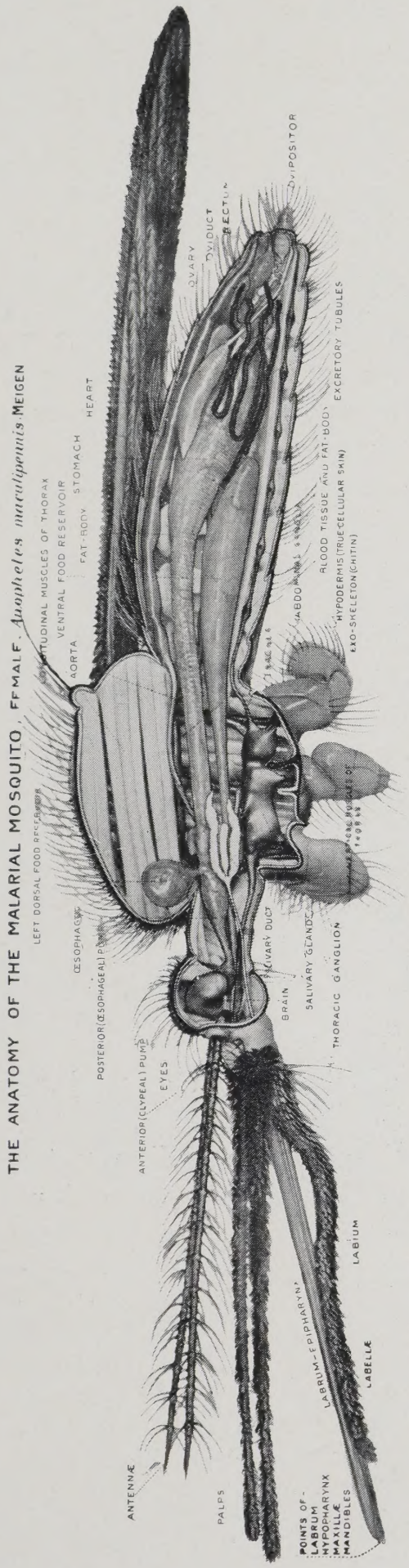


FIG. A. PHOTOGRAPH OF MODEL IN AMERICAN MUSEUM OF NATURAL HISTORY

mit malaria. The adult form (*imago*) of most species hibernates, and thus lives through the winter. The developmental phase of the parasite in man is called the "nonsexual cycle"; that in the mosquito, "the sexual cycle."

As stated above, there are three distinct species of the parasite, which differ in their microscopical appearance and also in their life-histories. These variations are partly responsible for the difference in the clinical symptoms resulting from malaria infection.

TERTIAN MALARIA (BENIGN)

The form of fever known as *tertian malaria* is caused by *Plasmodium vivax*. This organism requires 48 hours to mature in the red cell, when it sporulates, liberating its toxins and spores, which vary in number from 16 to 24. As the tertian organism approaches maturity in the red cell, it is larger than that of either of the other species. The normal dimensions of the red cell in which it develops become enlarged, and in consequence it is frequently caught in the minute blood vessels (capillaries) of the viscera, where sporulation generally takes place. The sporulating forms are therefore seldom seen in the peripheral blood (that obtained from the finger or ear) but must be sought for in the spleen, liver or other deep-seated viscera.

QUARTAN MALARIA (BENIGN)

The *quartan* type of malaria fever is caused by *Plasmodium ma-*

lariae. The organism differs from *Plasmodium vivax*, in that it takes 72 hours to mature instead of 48, and produces at maturity from 8 to 10 spores only. It is smaller than the tertian parasite and does not enlarge the red cell in which it develops. Consequently the pre-sporulating stage is frequently seen in the peripheral blood; it resembles a "rosette" or "daisy" in appearance, with the spores regularly grouped about the border of the red cell in which it developed.

Estivo-Autumnal, Sub-Tertian or Malignant-Tertian Malaria

This form of malaria is caused by *Plasmodium falciparum.* In Italy, where the seasons are well defined, *quartan* and *tertian* fevers are more prevalent in the spring and winter months, and *estivo-autumnal* in the summer and autumn months—hence the term *estivo-autumnal.* As most of the malignant forms of malaria are caused by *P. falciparum*, this type is sometimes called malignant tertian, or sub-tertian, because it has a tertian periodicity in its development similar to that of benign tertian, referred to above. Each estivo-autumnal parasite produces, on sporulation, from 24 to 32 spores. The male and female sexual forms (gametes) also differ from the gametes of the other species, in that they are crescent-shaped.

The estivo-autumnal parasite, during its sexual cycle in the female anopheles mosquito, is more susceptible to the influence of cold than the tertian and quartan types (frequently grouped together as the benign fevers), and hence is not as widely distributed geographically as the benign types, and occurs chiefly in the warmer regions of the Tropics and Sub-Tropics.

Incubation Period

When an individual is infected with malaria, several days elapse before symptoms develop. This interval is called the *period of "incubation,"* and varies considerably in length mainly according to two factors: (a) the species of parasite involved, and (b) the vital resistance of the patient, or the protective and defensive agencies of the body. A certain number of parasites must be present in the blood before symptoms appear. Manson-Bahr estimates that there must be at least one parasite to every 100,000 red-blood cells, or 50 parasites to every cubic millimeter of blood. The patient suffering from a moderately severe attack probably has approximately 500 parasites to the cubic millimeter of blood, and in very severe attacks 20 per cent or more of the red cells may harbor parasites—which is the equivalent of about 1,000,000 parasites for every cubic millimeter of blood. (Normally there are about 5,000,000 red cells to the cubic millimeter.)

The *Plasmodium vivax* parasites, which cause tertian fever, produce from 16 to 20 spores at each sporulation, every 48 hours, and generally about 2 weeks elapse between the period of infection and the production of symptoms.

The *Plasmodium malariae* parasites, which cause quartan malaria, produce 8 to 10 spores each, and sporulate every 72 hours, so that the period of incubation is approximately 3 weeks.

The *Plasmodium falciparum* parasites, which cause estivo-autumnal

FIG. 1. ANOPHELES EGGS (MAGNIFIED)

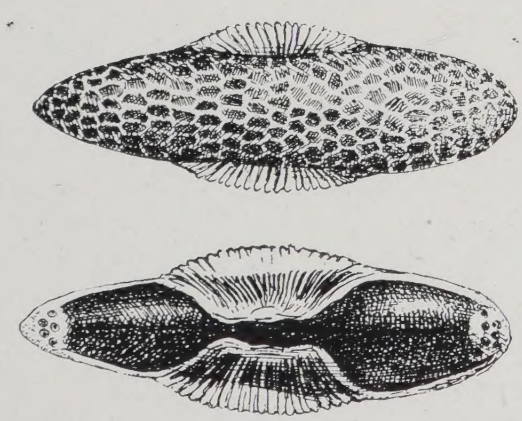


FIG. 2. ANOPHELES EGGS (GREATLY MAGNIFIED)

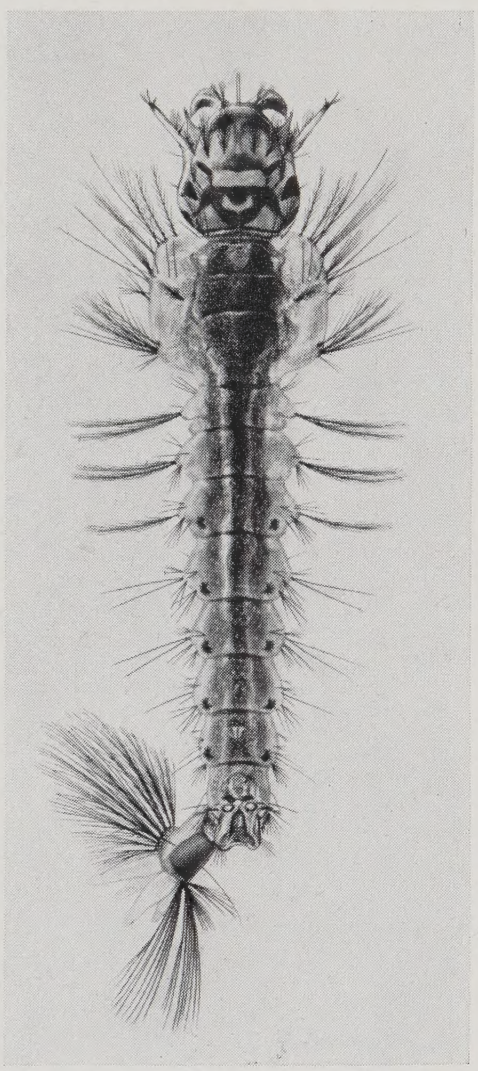


FIG. 3. LARVAE OF ANOPHELES PUNCTIPENNIS

Bureau of Entomology, U. S. Dept. of Agric., Wash., D. C.

fever, produce from 24 to 32 spores each, and sporulate every 48 hours, so that the period of incubation is from 8 to 12 days.

Some individuals are more susceptible to malaria infections than others; that is, the power of the body's defensive agents protecting against disease varies in different individuals to a marked degree, and for many reasons. This variation has an important influence in the onset of symptoms, which may be delayed for several days or weeks by these agents' resistance; and if that resistance is powerful enough,

FIG. 4. DIFFERENT STAGES IN THE DEVELOPMENT OF MOSQUITOES—CULEX (LEFT) ANOPHELES (RIGHT)
Note sitting postures of adults on grass blades.

Vittorio Ascoli

the parasite or its toxin is destroyed, and no symptoms develop--in other words, the patient is "*immune*."

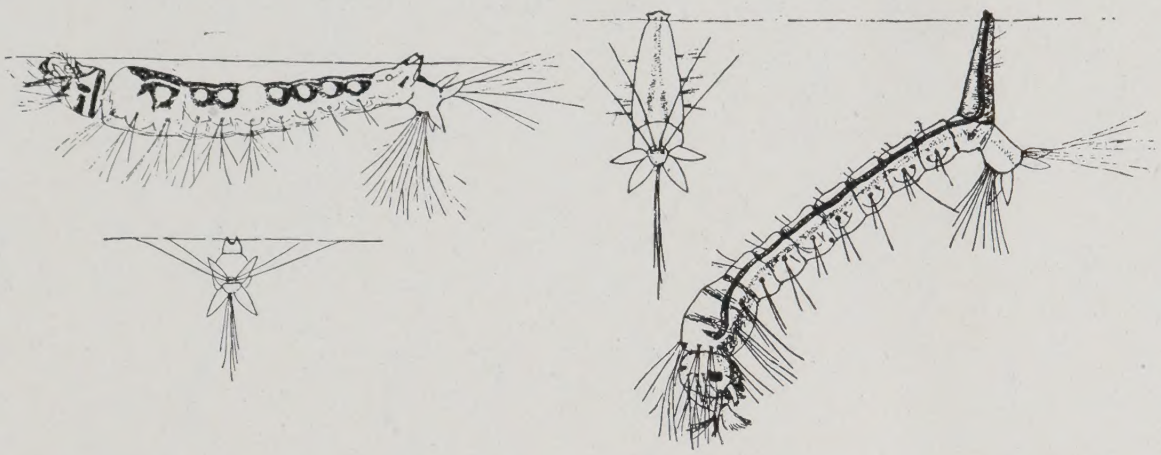


FIG. 5. RESTING POSITIONS OF LARVAE OF CULEX (RIGHT) AND ANOPHELES (LEFT)
Bureau of Entomology, U. S. Dept. of Agric., Wash., D. C.

SYMPTOMS

At each sporulation, along with the spores, toxin or poison is liberated, and this is chiefly responsible for the symptoms produced. The more parasites present, the more red cells invaded, and the more toxin produced. When there are about 50 parasites to the cubic millimeter of blood, the patients begin to have feelings of lassitude, nausea, headache, loss of appetite, bone-ache, vague muscular pains, and chilly sensations. At each succeeding sporulation all these symptoms increase until definite chills or rigors ensue.

The symptoms of the two benign types (tertian and quartan) are similar, except for periodicity. Those of the estivo-autumnal type differ materially from those of the benign. The rigor or chill charac-

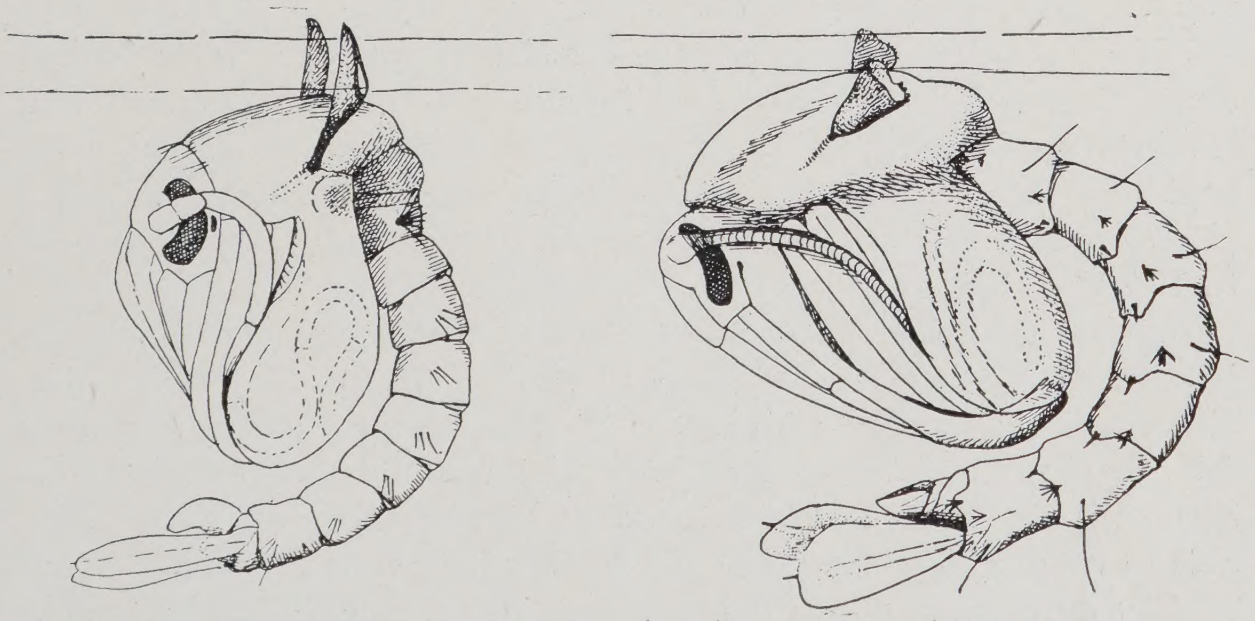


FIG. 6. PUPAE OF CULEX (LEFT) ANOPHELES (RIGHT)
Bureau of Entomology, U. S. Dept. of Agric., Wash., D. C.

teristic of the benign types of fever has three distinct phases which pass gradually from one to another. These are called respectively the "*cold*," "*hot*," and "*sweating*" stages of the febrile paroxysm.

The Cold Stage.—This sets in with chilly feelings over the body, gradually becoming more intense, so that the teeth chatter, the patient shivers, and heavy wraps or blankets are sought. Vomiting is usually present and may be distressing, and in children convulsions are frequently seen. There is a small, rapid pulse, the skin is cold and blue, and the condition known as "goose skin" is present. During this stage,

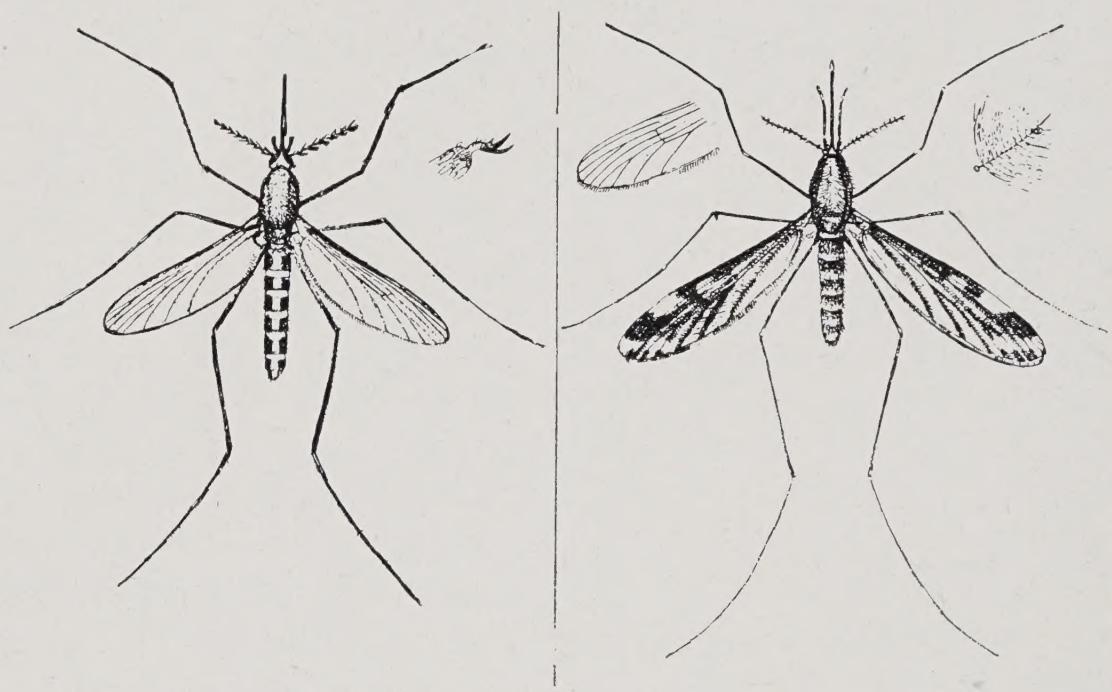


FIG. 7. (CULEX) AËDES SOLLICITANS ANOPHELES PUNCTIPENNIS
Bureau of Entomology, U. S. Dept. of Agric., Wash., D. C.

which lasts from 20 to 60 minutes, the body temperature rises gradually.

The Hot Stage.—In this stage the shivering ceases, warm feelings ensue, followed by sensations of intense heat and distress, so that blankets are discarded. Headache is severe, the face flushed, pulse rapid, full and bounding. The respiratory rate increases, vomiting is persistent, the skin hot and dry, and the temperature ranges from 103 to 106 F. This stage lasts from 1 to 2 hours.

Sweating Stage.—The hot stage is succeeded by the sweating stage, in which the patient breaks out into a profuse perspiration which literally saturates the bed clothing. The temperature, however, rapidly falls to normal, or sub-normal, and all the symptoms gradually subside until the patient feels tranquil and well, and believes that he is able to resume his work. This stage lasts from 2 to 4 hours.

The duration of all the three stages of the chill, or rigor, is variable, but generally lasts from 6 to 10 hours.

The above description of a rigor or *ague* attack applies particularly to tertian and quartan infections. They differ from each other mainly in the fact that in single infections the tertian chills recur every 48 hours, while the quartan chills recur every 72 hours.

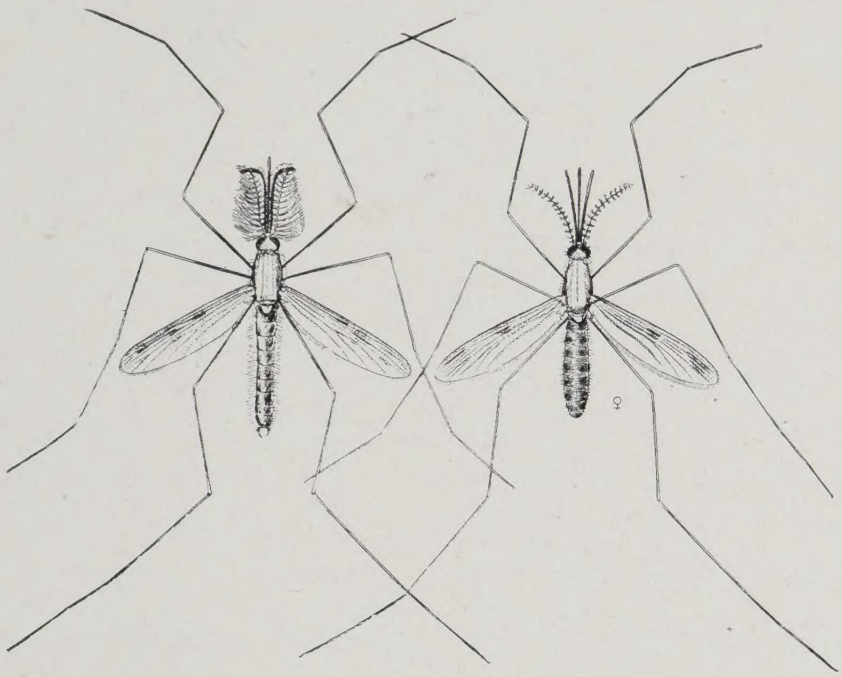


FIG. 8. ANOPHELES QUADRIMACULATUS — MALE AND FEMALE
Bureau of Entomology, U. S. Dept. of Agric., Wash., D. C.

The fever paroxysms of estivo-autumnal fever differ considerably from those of the benign types. The chills are not so definite, and often partake of the character of merely *chilly sensations*, and the duration of the *hot stage* lasts about 24 hours, generally with some small remissions of the fever during that period. The symptoms during the fever stage are very similar to those described in connection with the benign fever, but are probably more severe in character. The toxin produced by these organisms apparently is of a more virulent

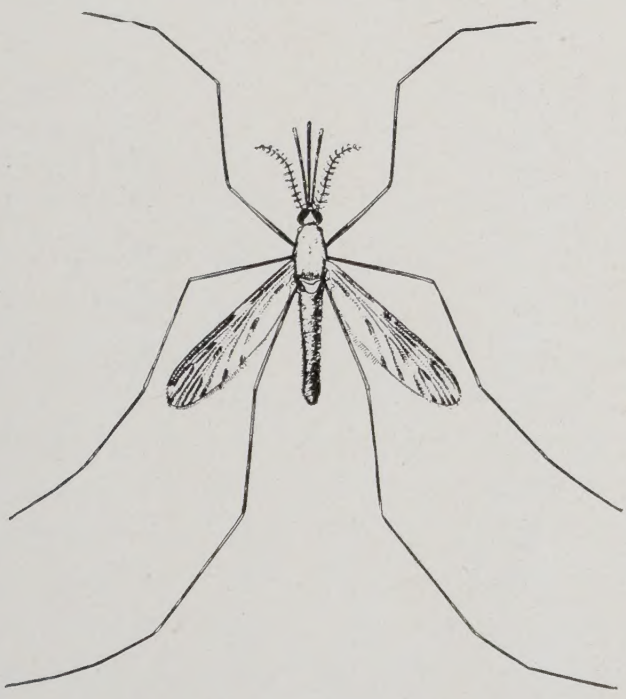


FIG. 9. ANOPHELES CRUCIANS—FEMALE

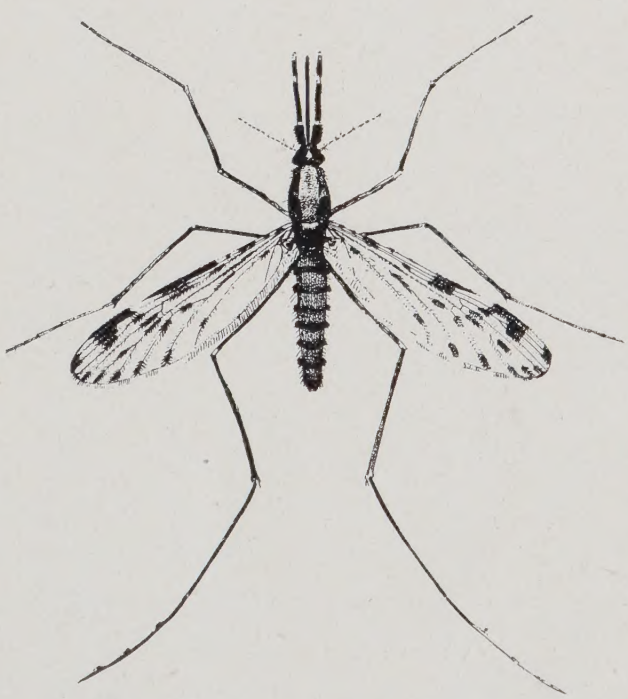


FIG. 10. ANOPHELES ARGYRITARSIS
Bureau of Entomology, U. S. Dept. of Agric., Wash., D. C.

nature than that of the benign types. The infected red cells tend to become plugged in the small blood-vessels (capillaries) of the viscera—intestinal mucous membrane, lungs, liver, kidneys, spleen, bone marrow and the brain—where they sporulate and cause local injuries and, consequently, symptoms referable to the respective viscera, the capillaries of which are plugged. The estivo-autumnal parasite is chiefly responsible for the malignant symptoms so often met with in malaria, and from this parasite the greater number of fatalities occurs. Wherever these parasites localize and sporulate, not only inflammatory conditions but frequently destruction of tissue (necrosis) will result. Hence we may have in these cases severe diarrhea, bronchitis, jaundice, nephritis; and—when they localize in the brain—coma, delirium, convulsions, paralytic conditions, etc., are prone to develop. In order to save life among this class of cases the treatment must be heroic and prompt.

Double and Mixed Infections

The symptoms, referred to above, in the different types of malaria are those of single infections. We may, however, have double or triple infections of any species of parasite, or mixed infections of the different species of parasites. Under these circumstances, the clinical picture, particularly the temperature charts, will vary greatly. Thus we may have not only daily paroxysms, but remittent or almost continuous high temperature, giving a clinical picture which resembles some other form of infectious disease. In all cases of malaria, however, careful examination of the blood will usually reveal the presence of parasites, but their presence does not negative the presence of some other infection also.

Blackwater Fever

Another clinical manifestation of malaria is *blackwater fever.* This is a manifestation generally of chronic untreated malaria, and most authorities believe that the estivo-autumnal parasites are chiefly responsible. In this condition the red cells of the blood are dissolved (*haemolysis*) and the colored contents (*haemoglobin*) are liberated in the blood stream. The destruction of red-blood cells may be so extensive that the liver, spleen and other organs that normally take care of the haemoglobin from worn-out or dead cells are unable to do so, and the excess amount of haemoglobin is excreted by the kidneys in such quantities that the normal color of the urine becomes red, and may be in such quantity as to give the urine a black color—hence the term "*blackwater.*" The kidneys are also very frequently affected through inflammation or obstruction by "haemoglobin casts," and may cease to function. About 10 to 20 per cent of blackwater fever cases die.

The prevention of blackwater fever rests in our ability to get rid of the malaria infection.

The onset of blackwater fever generally begins with a chill, followed by a high temperature, great prostration, thirst, vomiting, abdominal distress, aching loins, and great tenderness over the acutely-enlarged

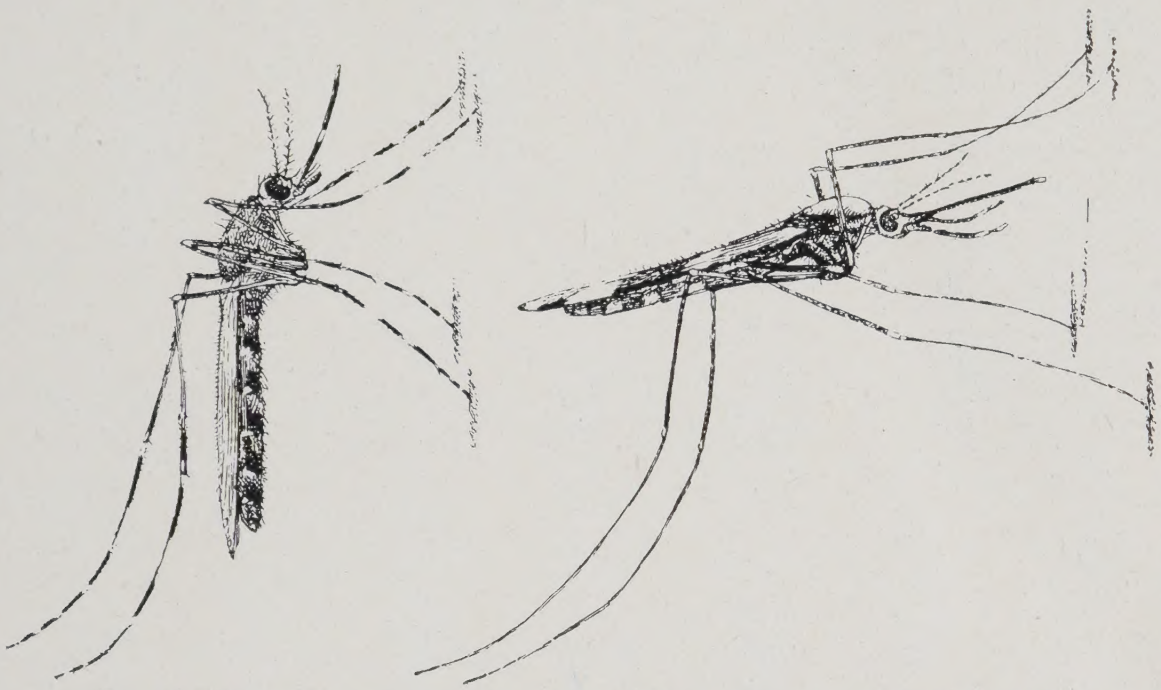


FIG. 11. RESTING POSITION OF CULEX (LEFT) AND ANOPHELES (RIGHT)
Bureau of Entomology, U. S. Dept. of Agric., Wash., D. C.

liver and spleen. The patient rapidly becomes jaundiced, and the urine that is passed varies in color from red to black. Following the chill, irregular fever usually persists for several days. The haemoglobin content of the blood may, in severe cases, drop to 10 per cent, or less, of the normal. There may be several attacks at intervals of one or more days, and they may result from exposure to cold or heat; from mental depression, fatigue, malnutrition, intercurrent disease; or from a dose of quinine.

IMMUNITY

By immunity, in malaria, is meant that the defensive or curative agents of the body are naturally so resistant to the parasites or their toxins—or have developed this power of resistance to such an extent—that no infection occurs, nor symptoms result, after the individual is bitten by infected mosquitoes. In the case of malaria there is no question but that immunity can be developed in some, if not in all, individuals. We meet with people apparently immune in all malaria-infected districts where tissues are so resistant that they will take care of any form of malarial infection that mosquitoes may transmit, so that no symptoms will result. If immunity, more or less complete, did not exist in malaria-infected districts, the population would soon be deci-

Plate A

SCHEMATIC REPRESENTATION OF MALARIA PARASITES

1 Parasite in red cell
2 Later stage
3 and 4 segmenting stages
5 Clump of pigment and spores in red cell ready to rupture
6 Female gamete
7 Male gamete
8 Male gamete in stomach of mosquito, throwing out flagella

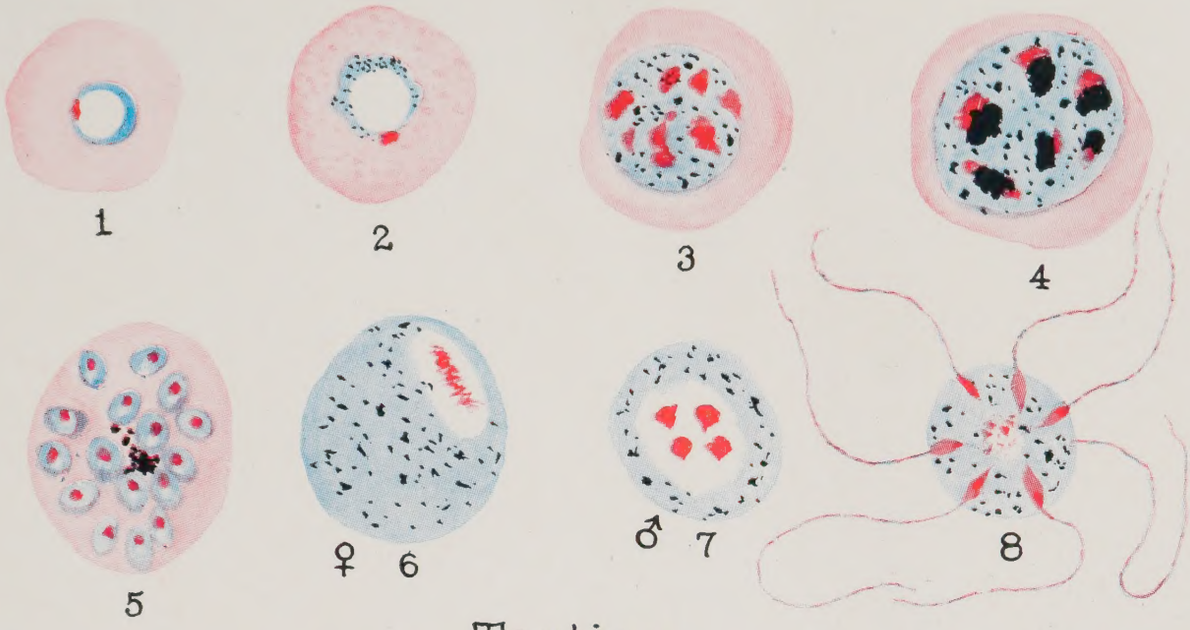
TERTIAN

1, 2, 3 stages of the parasite in the red cell
4 Daisy form showing segmentation
5 Liberated spores with small mass of black pigment
6 Female gamete
7 Male gamete
8 Male gamete in stomach of mosquito, throwing out flagella

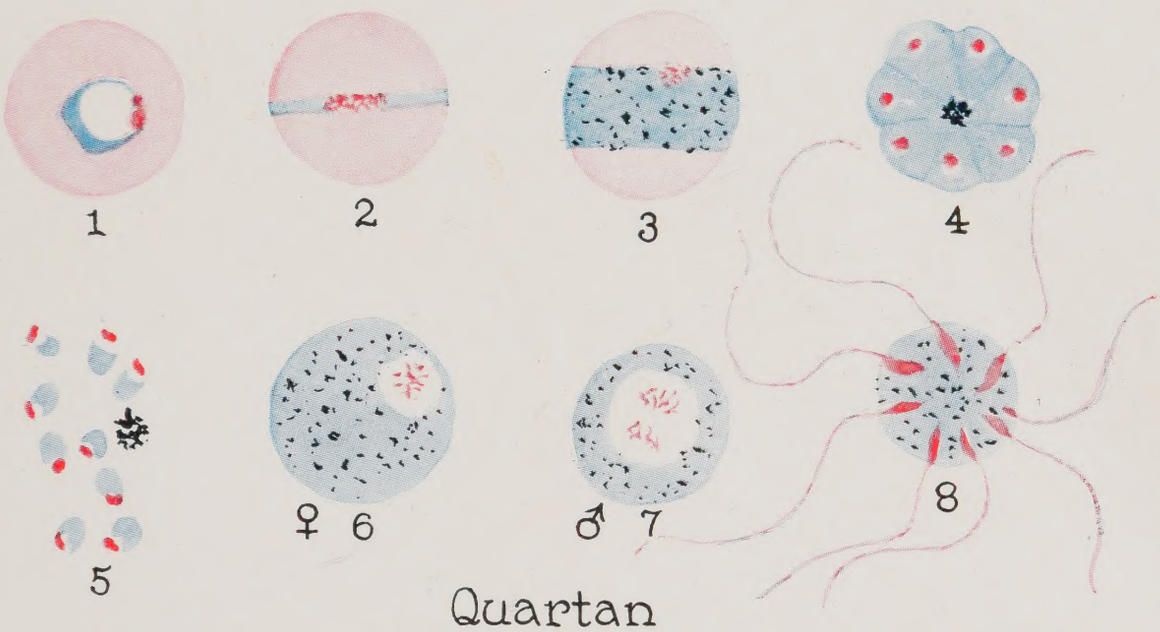
QUARTAN

1 Two small parasites on surface of red cell
2 Ring form of parasite partly in red cell
3 Later stage within cell
4 Clump of pigment and spores in red cell ready to rupture
5 Series of spores (disproportionally enlarged)
6 Female gamete (crescent)
7 Male gamete (crescent)
8 Male gamete in stomach of mosquito, throwing out flagella

AESTIVO-AUTUMNAL



Tertian



Quartan

Aestivo-autumnal

PLATE A

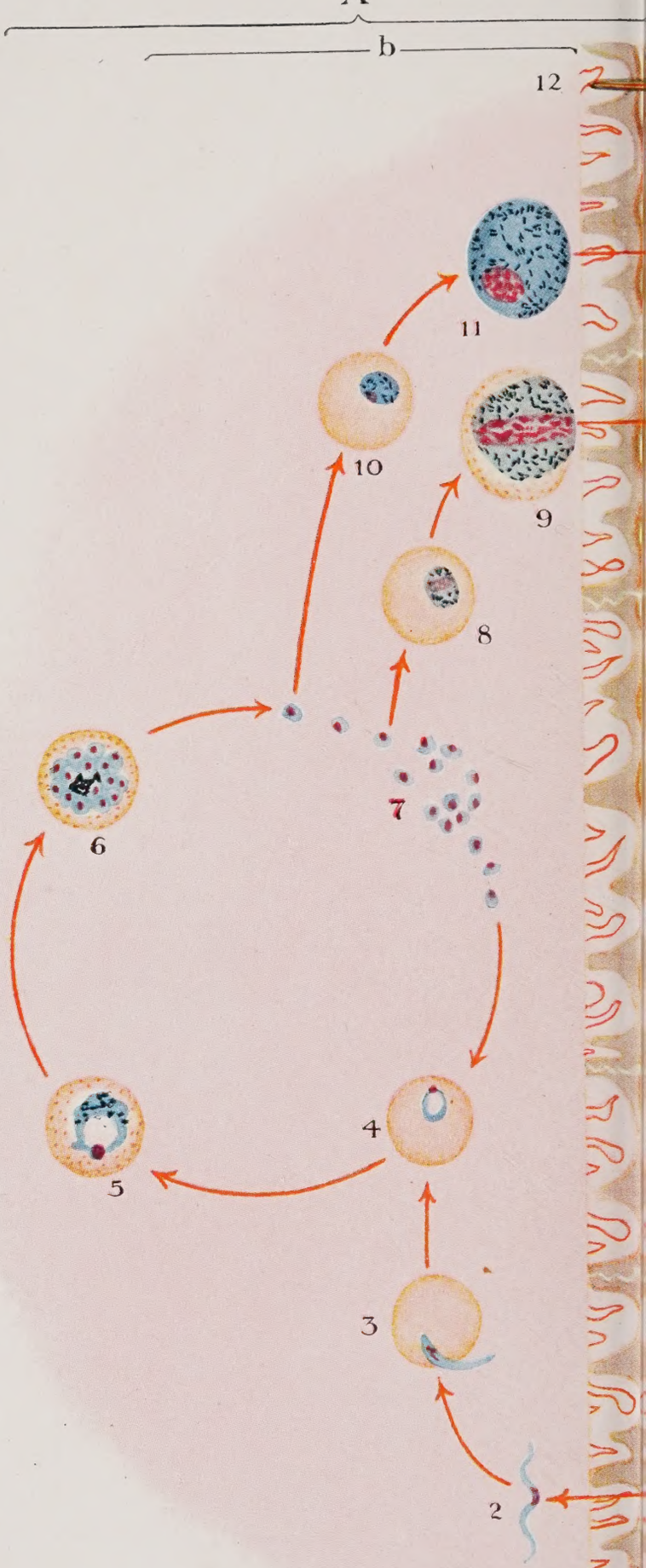
MABEL HEDGE, PINX.

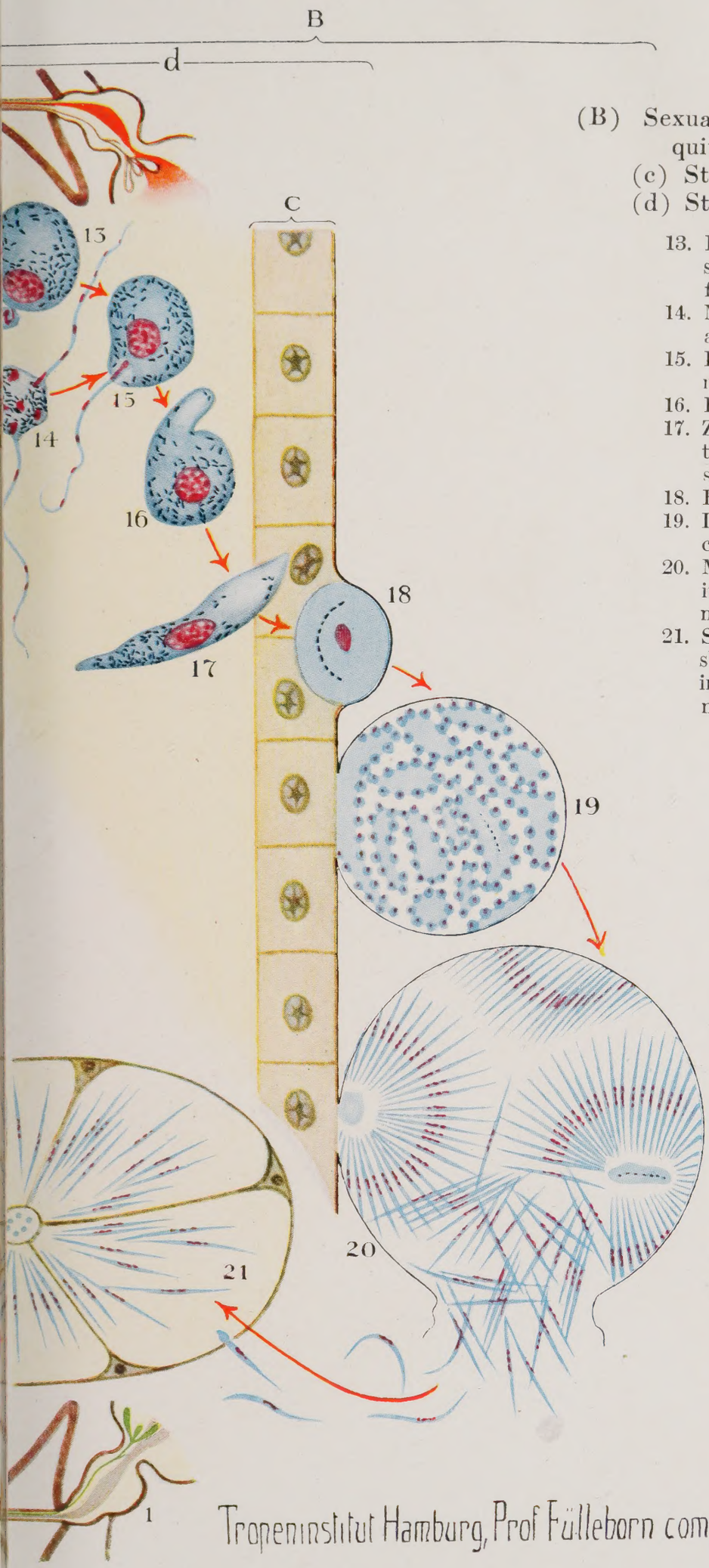
(A) Nonsexual cycle in the human host.

(a) Section of human skin showing different layers with loops of blood vessels (in red) and secretory ducts.

(b) Blood stream.

1. Head of mosquito with proboscis puncturing skin and injecting sporozoites into blood vessels. (The salivary gland and duct shown in green.)
2. Malarial sporozoite.
3. Sporozoite entering red-blood cell.
4. Red cell containing "signet-ring" form of parasite.
5. Developing parasite in red cell.
6. Parasite divided into spores.
7. Group of spores after sporulation, most of which enter other red-blood cells and continue the nonsexual cycle of development.
8. Red cell showing male gamete.
9. Male gamete fully developed.
10. Red cell showing female gamete.
11. Female gamete fully developed.
12. Mosquito's proboscis withdrawing infected blood.



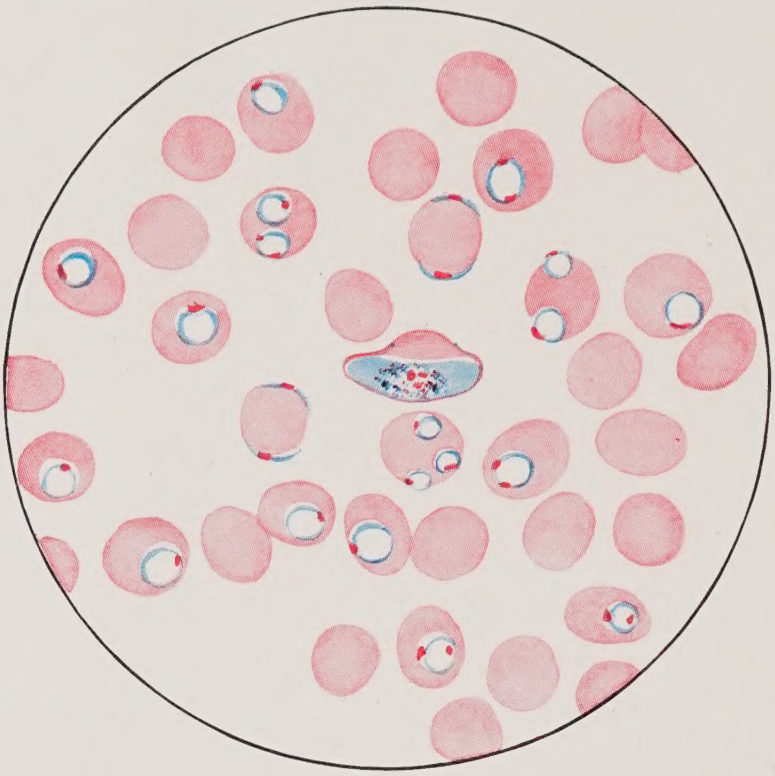


(B) Sexual cycle in the anopheles mosquito.
(c) Stomach wall of mosquito.
(d) Stomach of mosquito.

13. Female gamete in mosquito's stomach, throwing off polar body for reception of male element.
14. Male gamete in mosquito's stomach, throwing off flagella.
15. Flagellum from male entering female gamete.
16. Fertilized female gamete.
17. Zygote, or worm-like stage of fertilized gamete, boring into the stomach wall of mosquito.
18. Early stage of oöcyst.
19. Later stage of oöcyst, showing cell division.
20. Mature oöcyst filled with sporozoites rupturing into body cavity of mosquito.
21. Section through salivary gland showing sporozoites ready to be injected into human subject by female mosquito.

Tropeninstitut Hamburg, Prof Fülleborn comp.

PLATE B



SEVERE AESTIVO-AUTUMNAL INFECTION WITH DEVELOPING GAMETE IN CENTER OF THE FIELD

After photograph by J. G. Thomson

SCHEMATIC REPRESENTATION OF INFECTED SALIVARY GLAND SHOWING ELONGATED SPOROZOITES IN THE CELLS (PINK) AND THE DUCTS (PALE BLUE). THE PINK CELLS SHOW BLUE NUCLEI.

PLATE C

MABEL HEDGE, PINX.

mated. The factors which bring about immunity to malaria are unknown; if they were known, the problem of its eradication would soon be solved. It must also be kept in mind that immunity developed against one species of parasite does not prevent infection by other species.

In malaria-infected districts we meet with a certain percentage of people whose blood is apparently free from the parasites, although those same people are constantly exposed to malaria infection. Undoubtedly, in most cases they have acquired the disease in childhood and developed agencies in the body which prevent reinfection, after the manner of the immunity developed in people who have had scarlet fever, measles, whooping cough, etc. On the other hand, a large percentage of the population, particularly in the rural districts, have malarial organisms in their blood. This infection interferes with their efficiency, and under certain conditions becomes acute, producing symptoms which incapacitate them for work. Malarial organisms may exist in sufficient number in the blood, in these *latent* cases, to infect mosquitoes that feed on them, and they may thus be able to communicate the infection to others. In other words, latent cases are reservoirs of infection and a menace to the community in which they live.

In these *latent*, or *chronic*, cases there is anaemia and consequently poor resistance, and such cases are thus liable to develop other diseases.

Treatment

Any method of treatment, to be efficacious, must care for not only the acute primary infections, but also the chronic relapsing cases. The prevention and treatment of blackwater fever necessitates careful consideration.

Primary Infections

Recent work by Yorke and Macfie has shown that primary infections in individuals otherwise healthy are readily cured if promptly and efficiently treated. When it has been determined that malaria infection exists in an individual, administration of quinine in some form and in some way is indicated. Before its administration is begun—except in malignant cases where especially prompt measures are necessary—a preliminary dose of 3 grains of calomel, followed in 6 hours by 1 to 2 ounces of magnesium sulphate serves a useful purpose and facilitates the cure. A couple of hours after the calomel has been given, the administration of quinine can be initiated. The amount to be given will depend largely on the age, sex and weight of the individual, and also on the nature and the severity of the symptoms. For the average individual with moderately severe symptoms, 40 to 45 grains of quinine

daily, divided in 2 or 3 doses will suffice, and this treatment should be continued until the temperature is normal. A second dose of magnesium sulphate should then be given, and the quantity of quinine should be reduced to 30 grains daily divided in 2 or 3 doses; and this dosage should be continued until the patient's temperature has remained normal for from 5 to 7 days.

In cases of malaria, a generous diet should be ordered as soon as the desire for food returns, and the patient must not be permitted to return to work before his appetite has returned and he feels physically fit.

Other disease complicating conditions may delay the convalescence, and should therefore be considered in the treatment. Subsquently the patient should be advised to continue 10 grains of quinine, daily, for at least two weeks longer, or if there is much anaemia present, a combination of quinine, iron and strychnine is indicated for the same length of time, or longer. A suitable combination is Aiken's tonic tablets, each one containing the following components:

Quinine Sulphate	1	grain
Acid Arsenous	1/50	"
Strychnine Sulphate	1/50	"
Reduced Iron	2/3	"
Ext. Gentian	1/4	"

In the vast majority of cases, if this method of treatment be carefully followed out, there will be no subsequent relapse. We find that children can tolerate larger doses of quinine proportionately to their age, than adults. To a child under 1 year of age, ½ to 1 grain can be given 3 times daily, and in older children the dose can be increased 1 grain for each year of age, up to 8 or 10 years. In malignant cases 5 grains hypodermically may be given immediately, and repeated if necessary; after this it can be given by mouth.

Some authorities (Bass's Standard Treatment) believe that 30 grains daily are sufficient, as long as there is fever, to bring about convalescence, and that after the fever ceases 10 grains should be given daily for a period of 2 months or longer, according to its chronicity.

The writer believes that in the more temperate climates quinine is not tolerated as well as in the warmer climates, and that in the colder climates the drug is more apt to produce symptoms of discomfort such as ringing in the ears, deafness, nervousness, etc. These symptoms may be prevented, or relieved to some extent, by bromides.

It is immaterial, in the ordinary cases of malaria, whether the quinine be given in solid or liquid form, so long as it is *swallowed*, *re-*

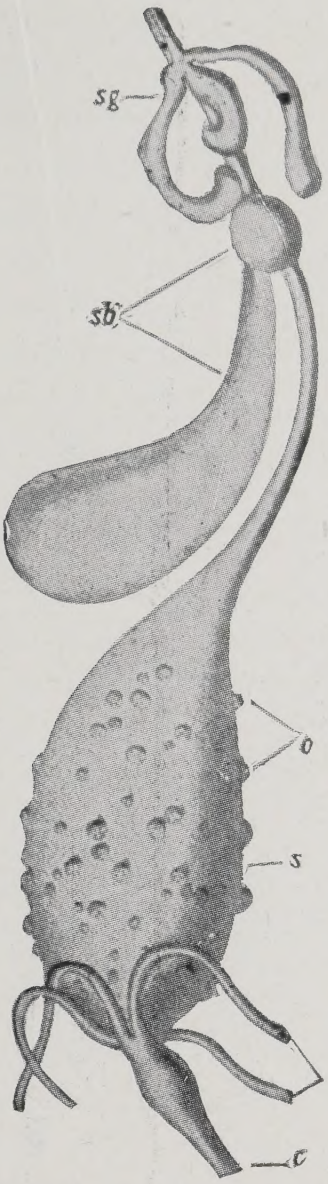


FIG. 12. DIGESTIVE TRACT OF *Anopheles*, THE STOMACH OF WHICH IS COVERED WITH NUMEROUS ZYGOTES, OR OÖCYSTS, OF *Plasmodium falciparum*: *c*, CLOACA; *mt*, MALPHIGIAN TUBULES; *o*, OÖCYST; *s*, STOMACH; *sb*, SUCKING BLADDERS, OR PUMPING ORGAN; *sg*, SALIVARY GLAND (STITT)

tained and absorbed. If vomiting occurs, quinine should be administered hypodermically.

ACUTE MALIGNANT CASES

We often meet with acute cases in which the treatment previously described will not save the life of the patient. Vomiting may be persistent,

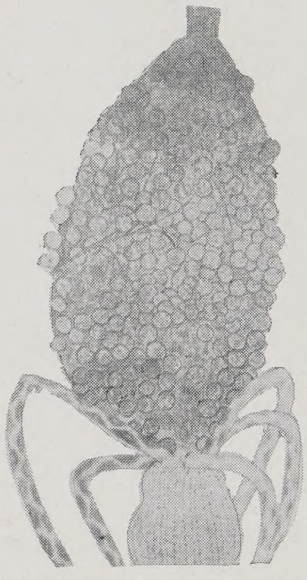


FIG. 13. STOMACH OF ANOPHELES SHOWING VERY MANY DEVELOPING OÖCYSTS

and the patient may be unable to retain anything. There may be coma, delirium, convulsions, paralysis, etc., resulting from the localization of the parasites in the small blood-vessels (capillaries) of the brain, and the patient may be unconscious or otherwise unable to swallow. In these cases quinine must be administered by means of the hypodermic needle, either intramuscularly or intravenously. The writer has also used the deep-subcutaneous method with gratifying results. By this method the needle should go down to the muscle sheath, but not into the muscles. The above-mentioned methods of administration require professional skill, and should be used only by a physician or a trained nurse.

Suitable preparations of quinine for hypodermic administration are now obtainable, and should be kept always ready for use in districts where this class of cases occurs. These preparations should be as nearly neutral as possible, or very faintly acid (Carter). A solution of excessive acidity will prove very painful and tend to cause destruction of the tissue where it is injected. The solutions for hypodermic purposes should also be properly diluted and slowly injected, and the location must be subsequently massaged, warm applications being used to accelerate absorption. The buttocks are to be preferred for intramuscular injections. For deep-subcutaneous injections the preferred sites are the buttocks, posterior to the pectoral muscle, or over the abdomen down to, but not into, the muscle sheath. For these injections the dilutions should be 1 of quinine to from 5 to 10 of diluent. For intravenous use the dilution should be greater—1 of quinine to from 10 to 20 of diluent; and some authorities advise a dilution of 1 gram of quinine to 100 and even 200 cc. of normal saline solution. It is very important, in giving intravenous injections, that the needle be very fine and the injections made very slowly.

In malignant cases, when any of these methods are used, 15 grains can be given, and can be repeated if necessary in 3 or 4 hours, until 3 or 4 injections shall have been given. In the case of intramuscular injections it is not wise to give more than 7½ grains in one location, and in subsequent administrations a location should be selected at least 4 inches from the site of the original injection. This precaution will tend to prevent the development of an abscess. As soon as the patient can tolerate quinine given by the stomach, hypodermics should be discontinued and the quinine should be given by mouth.

Chronic and Relapsing Cases

In these cases there is a different clinical picture, and the treatment must be varied accordingly. The patient has a chronic malaria infection because:

(1) The primary infection was never cured, not enough quinine having been taken over a sufficient period of time.

(2) The patient has some other complicating disease or organic infection which, in itself, is sufficient to lower his resistance, and thus prevent the defensive agencies of the body from developing immunity.

(3) The patient is suffering from malnutrition resulting from food deficient in quantity, quality, or both.

In the treatment of cases of chronic malaria these defects must be taken into consideration, and corrected as far as possible. In these chronic cases there is not only blood-destruction but impoverishment

of the coloring matter of the red-blood cells, as well. The treatment as described in primary infections should be given, but during the convalescent period the quinine, or the combination of it with iron and arsenic, should be continued over 3 or 4 months until the convalescence of the patient is completely established. In some of the more chronic relapsing cases a change of climate may prove to be very beneficial.

Treatment of Blackwater Fever

In these cases, owing to the distressing thirst and vomiting, immediate relief can best be obtained by injecting 8 to 10 ounces of warm, normal saline solution into the tissue. (Normal saline solution is made by dissolving a teaspoonful of common table-salt in a pint of warm water that has been boiled and allowed to cool to body temperature.) If suitable apparatus is not available for making this solution, a cleansing enema should first be given, and then 6 to 8 ounces of normal saline can be slowly introduced into the bowel through a high rectal tube. This treatment can be repeated every 3 or 4 hours; it will relieve the thirst and vomiting.

After the urine becomes normal in color and the stomach can tolerate fluids, a bland liquid diet can be taken by mouth. When the acute symptoms subside, a small dose of quinine (2 or 3 grains) should be given hypodermically. If this is not followed by a reappearance of black water in 3 or 4 hours, another hypodermic—of 5 grains—can be given. Then, if that is tolerated without any disagreeable results, a small dose (5 grains) of quinine 3 times daily can be given by mouth, and the amount can be gradually increased until the treatment is similar to that described for primary infections.

Dr. A. A. Facio, of Port Limon, Costa Rica, has obtained excellent results in these cases by giving intramuscular injections of 3 grains of caffeine sodio-benzoate twice daily for 2 or 3 days, and then once daily until the jaundice disappears.

Dr. Crawford, of Sasser, Georgia, recommends an intravenous injection of 20 cc. of anti-streptococcus serum, to be repeated if necessary.

Unfortunately, from 10 to 20 per cent of blackwater cases die. In some of these cases, the red cells continue to dissolve, and the patients continue to pass black urine until they literally bleed to death. In other cases, the secreting tubules of the kidneys become diseased, and the coloring matter of the blood (haemoglobin) forms casts in the tubules, the secretion and passage of urine being prevented. These latter cases develop uraemia and die shortly after the suppression of urine.

We know of no remedies to prevent or relieve such conditions. *The importance of seeking skilled professional advice in the treatment of*

all severe forms of malaria must be stressed. Delay in seeking advice may prove fatal to the patient.

Quinine Prophylaxis

Recent developments in the study of malaria would seem to indicate that quinine given to a person exposed to malaria will not prevent infection, but that if it be taken routinely during periods of exposure, and infection occurs, the routine administration of quinine in sufficient quantities for from 10 to 14 days after infection, will prevent the development of symptoms. In other words, quinine has no effect on the sporozoites injected into the blood by infected mosquitoes; and some authorities believe that it has no effect on the spores (*schizonts*) liberated in the blood stream after sporulation, but only on the organisms (trophozoites) enclosed in the red-blood cells.

It would seem useless, therefore, to give quinine to prevent malarial infection. However, as soon as infection manifests itself by the development of symptoms, quinine should be given in generous quantities. Under these conditions there is a "primary infection," which should be treated as such. If insufficient quinine is given for an insufficient period the affection becomes chronic, and therefore difficult to cure, and the possibility of the development of blackwater fever occurs. In communities where infection is widespread the administration of quinine is strongly indicated, and it should be given daily or interruptedly, over long periods. This is particularly to be recommended if infected anopheles mosquitoes are very numerous in the neighborhood of dwellings. Controlling the development of the infection will prevent a great deal of sickness, and also tend to prevent mosquitoes from becoming infected, so that the spread of the disease will be limited.

It is advisable to give consideration both to the preparations of quinine that should be used, and to the best methods of administration. As to the first—we may administer quinine in the form of the insoluble alkaloid, or its salts, the sulphate, bi-sulphate, hydrochloride, or bihydrochloride. Some also recommend the tannate, tartrate, or lactate salts, as well as euquinine (an ethyl-ester of quinine-carbonic acid). This latter group of preparations is practically insoluble, hence almost tasteless, and consequently of value in selected cases. The quinine alkaloid is also practically insoluble. The sulphate is soluble to the extent of 1 part in 800 parts of water, and the hydrochloride to the extent of 1 part in 35 parts of water. When acid is present in excess, these salts enter into solution readily: the bisulphate 1 in 18 parts, and the bihydrochloride in less than its own weight in water.

For hypodermic use, the bihydrochloride salt is to be preferred be-

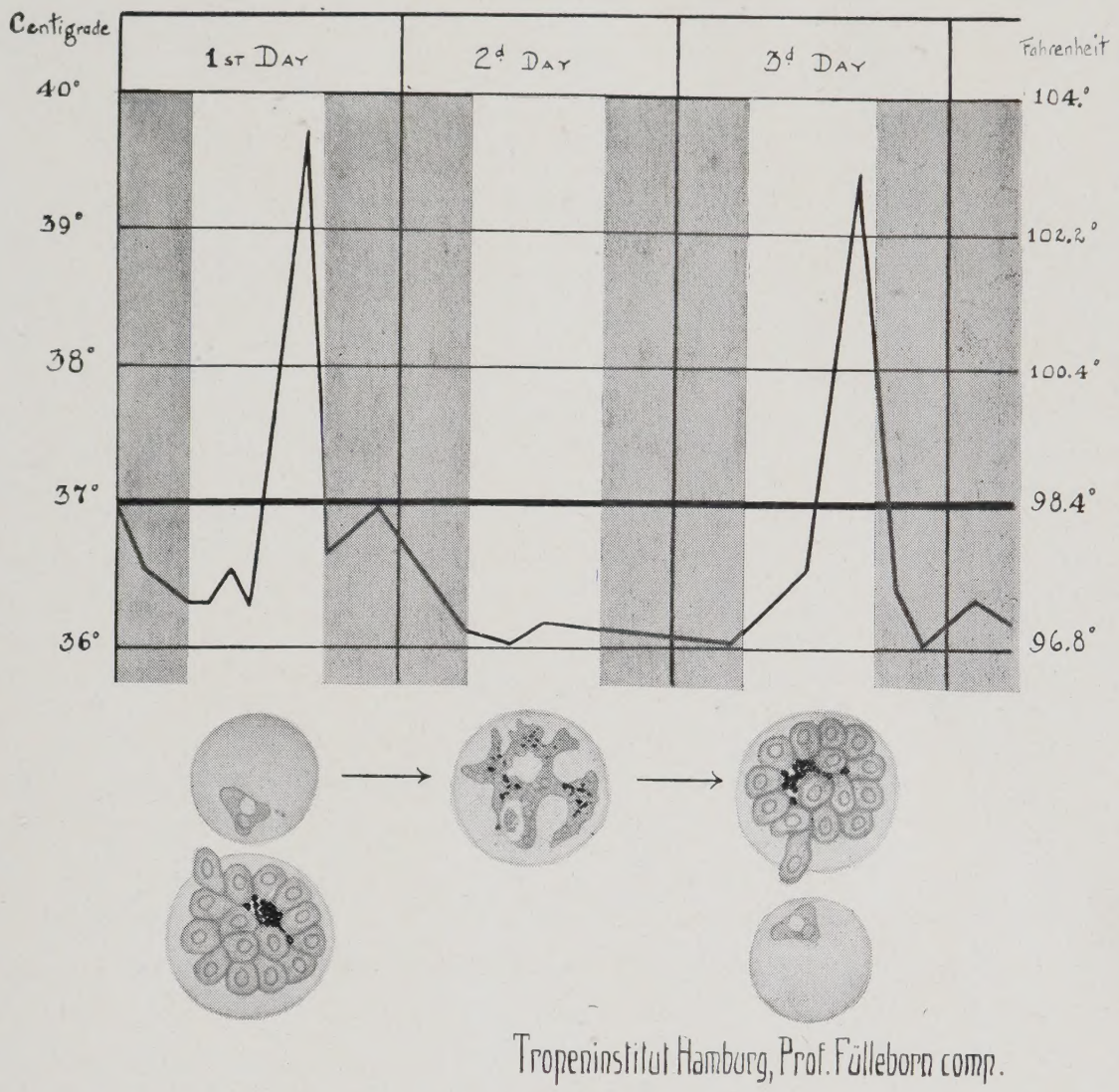


FIG. 14. TEMPERATURE CHART OF TYPICAL TERTIAN MALARIA TEMPERATURE AND, BENEATH, THE STAGES OF THE MALARIA ORGANISMS CORRESPONDING TO THE FEBRILE CURVE

cause of its solubility, but if the solution contains an excess of acid the injection is very painful. It is better, therefore, to use the neutral salt, *well diluted*, at body temperature, and to administer it *very slowly*.

From observations made recently in our hospitals, the insoluble salts of quinine are as effective therapeutically as the soluble preparations. It is generally believed, however, that quinine in *solution* acts more *quickly* than in the *insoluble* preparations. Solutions must also be used with patients who are unable to swallow pills, tablets or capsules. Care must always be taken to see that pills and tablets are readily friable, for otherwise they will pass through the alimentary tract without being absorbed.

Undoubtedly the intravenous use of quinine is indicated, and is to be preferred, when *prompt* action is necessary in order to *save life*. Howell claims that it takes about half a minute for a circulating particle of blood to return to any one starting point, and as the intravenous injection requires a longer time than this, all infected circulat-

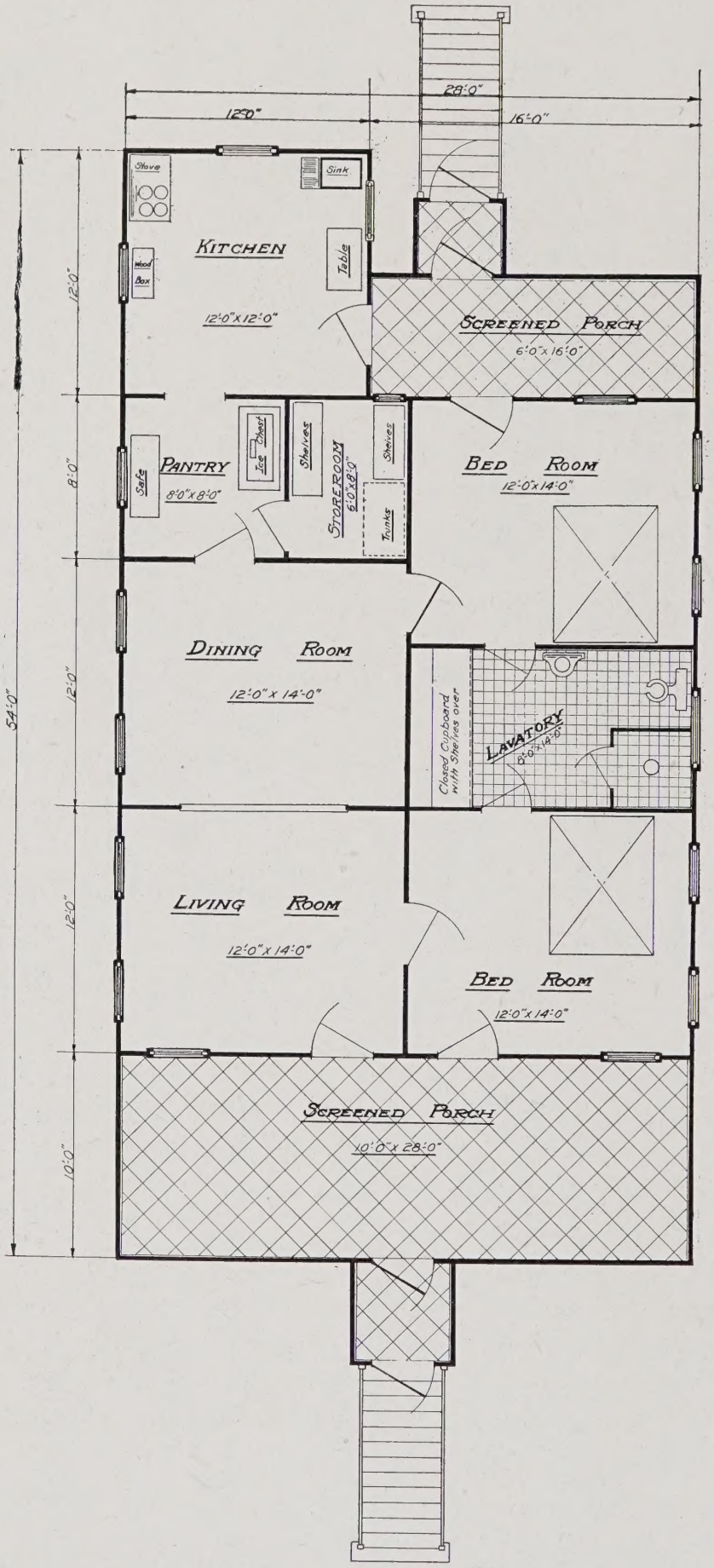


FIG. 15. FLOOR PLAN OF HOUSE OPPOSITE

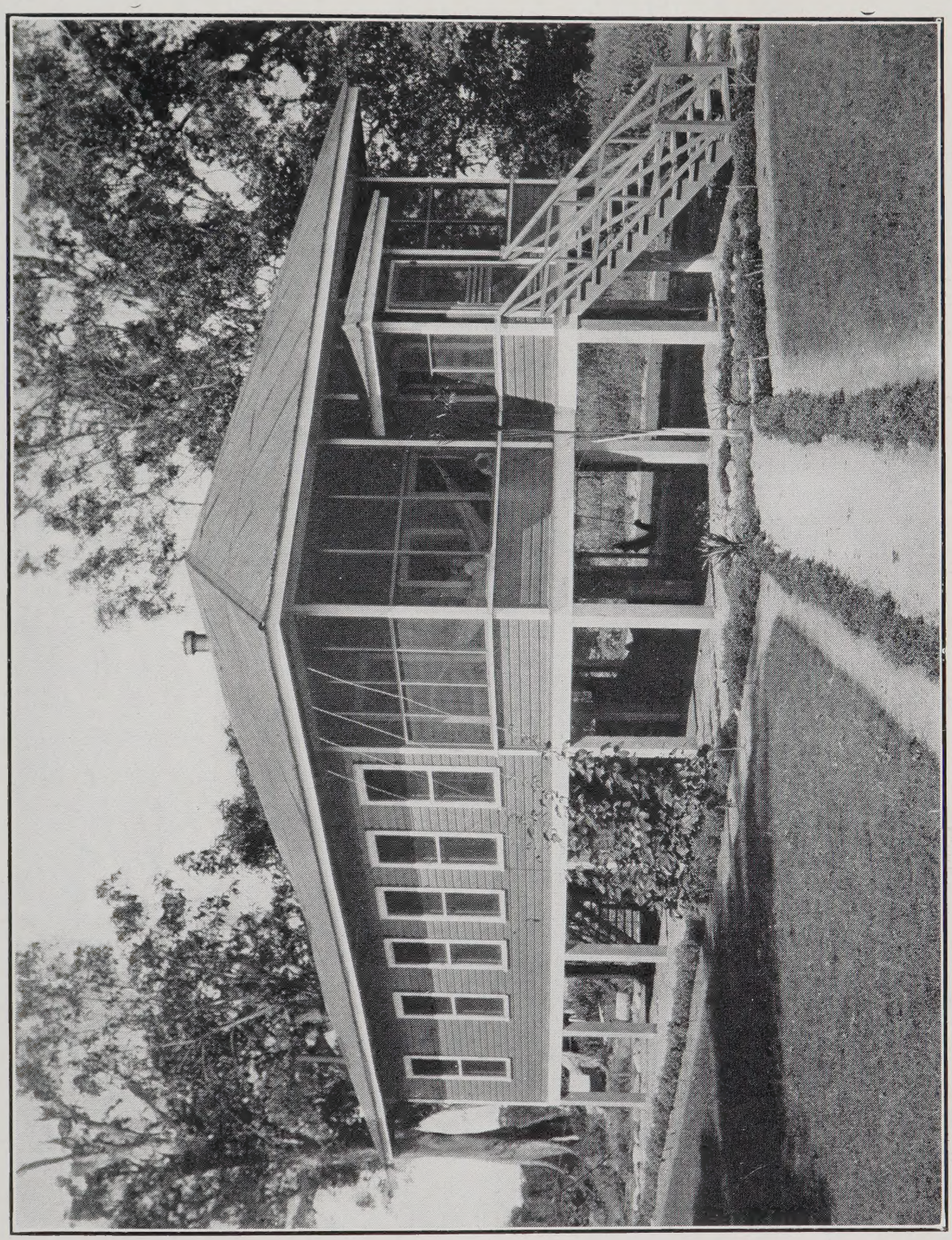


FIG. 16. PROPERLY SCREENED HOUSE

ing cells are brought into direct contact with the quinine solution during the period of injection, and only those escape which are plugged in the capillaries of the viscera.

Prevention of Malaria

To avoid being bitten by malaria-infected mosquitoes, is to prevent malaria. The female anopheles mosquito lays her eggs on the surface of fresh or brackish water in star, triangle or ribbon patterns, about 100 or more during each egg-laying period. The temperature of the water will largely determine the length of time (12 to 72 hours) in which the eggs hatch into larvae or "wiggle-tails." The larvae feed on all forms of vegetable matter, and complete this stage of their growth in approximately from 3 to 8 days. They then enter the resting, or *pupa*, stage during which time they complete their development and emerge as adult mosquitoes, or *imagoes*, in from 2 to 3 days. The length of time necessary for the egg to reach maturity, from the time it is laid, is from 1 to 3 weeks according to the temperature of the water and other factors affecting nutrition.

Cold retards and warmth hastens the development. About 24 hours after mating and fertilization the adult female seeks a meal of warm blood to mature the eggs. If she feeds upon malaria-infected individuals and ingests the sexual malaria parasites she becomes infected, and in about 10 or 12 days is ready to infect the next individual on whom she feeds. The mosquito's first "feed" of warm blood does no harm to the individual bitten, but when the insect's salivary glands are full of the young, malaria rod-like spores (*sporozoites*) she is dangerous. Our efforts, therefore, must be directed to prevent her feeding upon us, or to encompass her destruction. Sanitary measures for prevention of malaria are directed, first, toward protection against being bitten, and secondly, toward destruction of the adult mosquitoes during their developmental or larval stage.

The female anopheles mosquitoes feed almost always between sunset and sunrise. To avoid being bitten by them, we must protect ourselves especially during these hours. The most satisfactory method of protection is to live in an effectively screened house. The writer believes that a poorly screened house is worse than one entirely unscreened, as it forms a mosquito trap from which the mosquito, having gained entrance, has difficulty in escaping, and thus repeatedly feeds on the inmates, if water is available. Very few carpenters employed for the screening of buildings thoroughly understand the requirements, and consequently their work is imperfect. It is very important to have a skilled inspector examine this work if satisfactory results are to be insured.

A mosquito-proof house is one which no mosquitoes can enter except through the doors, and these should always be protected by porches screened separately from the veranda or main entrance to the house. The porches should be on the windward or exposed side of the house, whenever possible, and the doors must be constructed to swing outward. The windows should be solidly and securely screened—the screens immovable and flush with the outside walls of the house. The

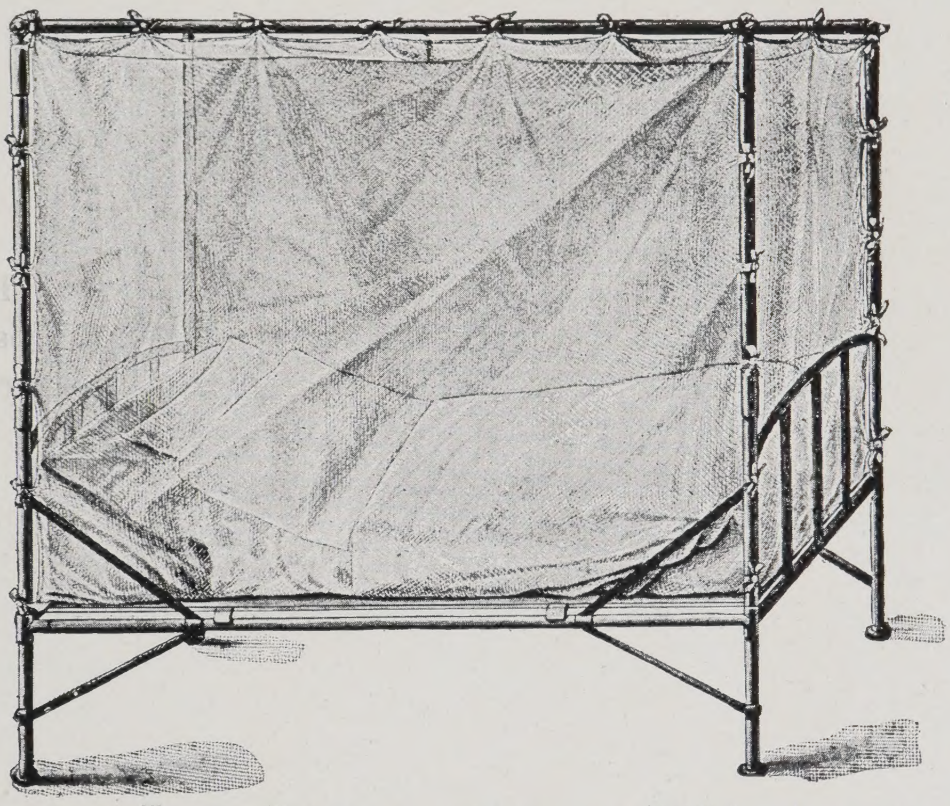


Fig. 17. Effective mosquito bar (*Fülleborn*)

windows, moreover, should be of the French type, opening inward, so as to admit of being easily cleaned. Shades, shutters, etc., should be arranged on the *inside* of the screening.

A ceiling is absolutely necessary. It is practically impossible to effectively screen a house that has no ceiling. Also, a ceiling prevents overhead heat-radiation and consequent discomfort, particularly in houses with metal roofs. Seasoned lumber should always be used in the construction of wood houses, or cracks will develop as the lumber dries, and thus render the screening measure ineffective. The screens should have a mesh of not less than 16 to 18 meshes to the inch, according to the gauge of the wire used in their construction. For the former size the wire gauge should have a diameter of .016 of an inch; for the latter .010125 (English standard). The gauze material should be of bronze, galvanized iron, copper, or monel metal. When exposed to sea air, pure copper or monel-metal wire alone is durable. The copper should not contain more than one-half of one per cent of iron. A screened house having been properly constructed, it is very important

for the inmates to realize that they must remain behind the screens from sunset to sunrise, or take other measures for protection, such as the use of repellants.

Next best to a screened house, the most effective method of protection will be mosquito bars over the beds. These also call for careful construction. They should never be less than 3 feet in width—otherwise it is practically impossible to prevent some part of the body from coming in contact with the net and thus being bitten through its meshes. The bars should be constructed and suspended so as to take the form of an inverted sack, the open end being securely fastened to the floor, or carefully tucked beneath the mattress of the bed.

According to Dr. Coogle, creosote sprayed throughout the dwelling is a satisfactory repellant for mosquitoes. This appears to be a good temporary measure in dwellings that do not lend themselves to effective screening; or if an individual is liable to be exposed at night, then some repellant sprayed on the clothing will prove temporarily effective. In a similar manner other essential volatile oils are recommended, but they are not very satisfactory.

Whenever possible, mosquitoes should be destroyed or their breeding prevented. Any attempt to destroy all adult mosquitoes is futile. Those accessible in the house can be destroyed, when "swatting" proves a satisfactory measure; and as they usually select dark places and avoid light, colored surfaces, they can easily be discovered. The services of children can readily be enlisted for this purpose.

Efforts therefore must be directed to prevent mosquitoes from breeding, or to destroy the larvae. As they lay their eggs in water collections of all sorts—ponds, streams, holes, seepage areas, discarded utensils, cans, etc.—in fact, in any place that will hold water or moisture for a week, the task of entirely preventing them from breeding is gigantic, and the best that one can hope for is a reasonable degree of control. In towns and cities there is no excuse for permitting mosquitoes to breed if ordinary vigilance is used and efficient sanitary measures are taken.

In villages and rural communities, reasonable control measures are almost always possible, and should be attempted. All useless rubbish, discarded cans, bottles, etc., which will hold water for a week should be destroyed or buried. Still water such as pools, etc., should be drained or filled whenever possible. When this is impossible they should be treated periodically with crude oil or some of its derivatives, Paris green, etc. There are a great many combinations of crude oil which are serviceable. In itself, it is too thick to spread in a satisfactory manner over the surface unless it is diluted with kerosene, castor oil or similar preparation. Good results are obtained by heating crude

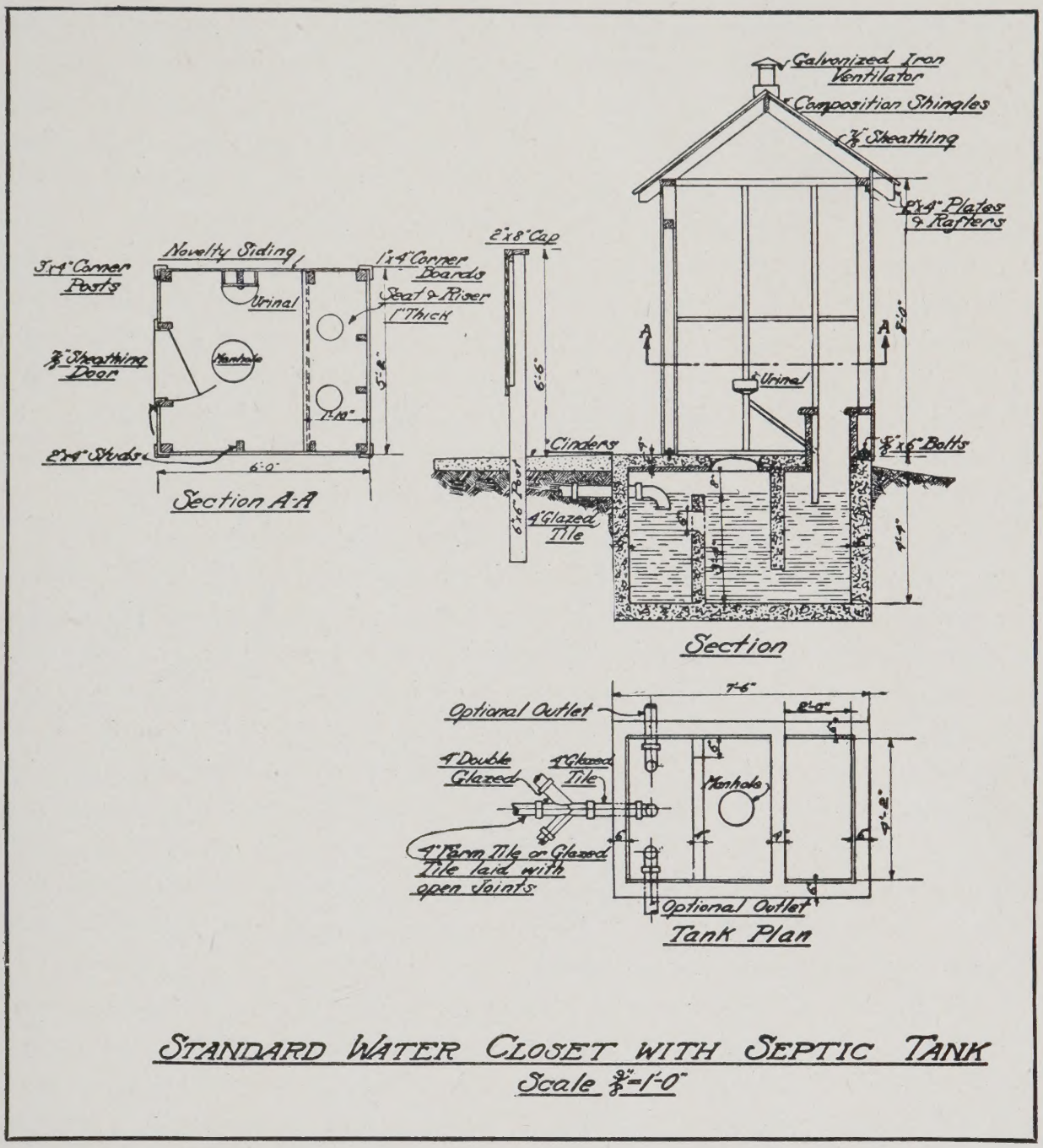


FIG. 18. STANDARD WATER CLOSET WITH SEPTIC TANK

oil before spraying it. Paris green should be mixed with any form of dust, in the proportion of 1 to 100, and thrown into the air on the windward side of the pond. It will thus be distributed over the water in a thin layer. One pound of the mixture is sufficient to cover approximately 1,000 square feet of water surface. The method proves very effective in destroying the larvae of anopheles mosquitoes, as they feed from the surface of the water and thus are readily poisoned. The method is particularly satisfactory as compared with the oiling of ponds or pools covered with vegetation; the powder settling on the leaves is gradually spread to the water beneath.

In ponds or pools which cannot be drained, and which are comparatively free from vegetation, fish-stocking with minnows is particu-

larly efficient. Gambusiae are generally used for this purpose, as they are "top-feeders" and consume large numbers of larvae from the surface. The edges of the pond should be kept clear of vegetation and the surface free from floatage. Wild shrubbery or rank vegetation should not be permitted to grow near the habitations, but should be cut from time to time to prevent the harboring of mosquitoes.

The water supply is important. When carefully banked wells are not available and cisterns must be used, they should be carefully screened. This screening necessitates a mosquito-proof cover, as well as aeration. Reinforced concrete is the best material for construction, as it is permanent and inexpensively maintained. If a solid roof is constructed an automatic closing-inlet is necessary, and a screened space beneath the roof for purposes of ventilation.

Special attention should be given also to latrines, to see that they are properly constructed and kept in a sanitary condition. This is necessary to prevent not only the breeding of mosquitoes, but the access of flies, which may communicate typhoid fever, dysentery, etc., as they feed from latrines which frequently contain disease-producing germs; then the flies visit food supplies, expel the contents of their infected probosces, and feed again. In localities where malaria is endemic, hookworm disease generally prevails also, and the two conditions are frequently present in the same individual. As hookworm disease produces anaemia, and since this lowers the resistance of the patient, the cure of the associated malaria infection is rendered much more difficult than otherwise would be the case.

In general, it may be said that malaria and hookworm disease are the handmaids of poverty and ignorance, and that their eradication depends on the development of prosperity among the inhabitants and the spread of knowledge of the causation and prevention of these diseases. Therefore, in a community any efforts directed toward the betterment of these conditions will tend to lower the incidence of the diseases mentioned.

Not only should schools be established in the communities where these diseases prevail, but a part of the school curriculum should be devoted to the teaching of the causation of the prevailing endemic and epidemic diseases, and the explanation of sanitary methods necessary for their prevention and cure. In this way, besides having one sanitary officer in a district, every school child, and through them their parents, might become sanitary officers for the protection of themselves and the community at large. We should endeavor to help the individual and to encourage him to help himself. Thus, and thus only, may we hope for efficient control and for the ultimate eradication of malaria and hookworm disease.

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